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Complete List of Authors:	Kuijper, Bram; University of Exeter College of Life and Environmental Sciences, Environment and Sustainability Institute
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**Developing differences: early-life effects and evolutionary medicine**

Bram Kuijper, Mark A. Hanson, Emma I. K. Vitikainen, Harry H. Marshall, Susan E. Ozanne, Michael A. Cant

**Abstract**

Variation in early life conditions can trigger developmental switches that lead to predictable individual differences in adult behaviour and physiology. Despite evidence for such early life effects being widespread both in humans and throughout the animal kingdom, the evolutionary causes and consequences of this developmental plasticity remain unclear. The current issue aims to bring together studies of early life effects from the fields of both evolutionary ecology and biomedicine to synthesise and advance current knowledge of how information is used during development, the mechanisms involved, and how early life effects evolved.

## Introduction

This special issue grew out of a meeting held in September 2015 in Falmouth, Cornwall, UK, which brought together rough equal numbers of evolutionary and biomedical researchers working on early-life effects. In both these fields, researchers have repeatedly demonstrated that experiences during early development can trigger developmental switches that shape physiology and behaviour for a lifetime, while potentially also affecting future generations [1–3]. In medicine, developmental plasticity in response to various early-life exposures lies at the heart of many non-communicable diseases, including cardiovascular and metabolic diseases (e.g., hypertension, obesity and type 2 diabetes), cancer and neurological conditions [2,4,5]. Understanding the nature of these plastic responses is therefore of huge social and economic importance.

In evolutionary biology, a substantial amount of thought has been devoted to understanding how natural selection has come to favour plastic responses and what consequences this has [6–8]: indeed, questions highly relevant to medicine -- such as why organisms respond to certain environmental stimuli while ignoring others [9,10], why they would remain sensitive to some stimuli much longer than to others [11–13] and how exposure to novel environments affects development [14,15] – are all mainstays in evolutionary theory, with rigorous modelling leading to testable predictions (e.g., review [16] in this issue). Moreover, evolutionary theory also accommodates for recent findings in which the developmental environment influences subsequent generations [10,17,18], for example when mediated through heritable epigenetic variants (see [19,20] this issue).

Our goal for the meeting was to explore what evolutionary and medical researchers could learn from the different findings and approaches in each other's fields. Conventionally, early-

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life effects in medicine have been studied with a strong focus on the mechanisms that underlie each of these pathologies in question. While insightful, an exclusively descriptive and mechanistic agenda is less likely to provide us with an understanding *why* early-life exposures have the effects that they have, which is crucial to identify the most effective ways of mitigation and to make sense of the large amounts of variation in responses within a population [21–24]. As shown above in the context of plasticity, ‘why’ questions are the meat and drink of evolutionary biologists.

For evolutionary researchers, medical research on model organisms and humans brings a richness of detail on the workings of development and individual phenotypic variation that is usually missing from biological studies. Moreover, biomedical research forces evolutionary biologists to think about pathologies and constraints on development, the information available to organisms at different stages of their life history, and the difficulties associated with forecasting the future. Natural selection is a process for maximising (inclusive) fitness [25], but this is very much a constrained optimisation problem – bounded by physical and energetic constraints imposed by the ecological and social environment, by constraints on information, and by the apparatus of genetic and cellular machinery. Medical research offers hugely powerful insights into the workings and constraints of developmental processes and their phenotypic consequences.

Following on from calls by others [23,26,27], this special issue therefore aims to place the study of early-life effects within the growing field of evolutionary medicine, which focuses on the question *why* the body becomes susceptible to disease [23,24]. Above and beyond mechanistic studies, evolutionary medicine provides two key insights to the study of pathology: first, natural selection on a certain trait serves to enhance the number of

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3 descendants, rather than health or survival [23,24]. Second, the response of traits to natural  
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5 selection is limited by a variety of constraints [28], particularly as natural selection acts not  
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7 on single traits, but on suites of traits which often have a shared genetic or developmental  
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9 architecture (pleiotropy) [29]. Taking these evolutionary viewpoints to the study of early-life  
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11 effects is important, as it allows one to consider that certain adverse health outcomes that are  
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13 nonetheless associated with high reproductive success can become prevalent in some  
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17 populations.

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21 In studying the evolutionary origins of early-life effects, evolutionary medicine is necessarily  
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23 *integrative*, as it (i) is based on a rigorous mathematical theory of evolution that describes  
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25 how natural selection acts on phenotypic variation. It does so by (ii) considering how  
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27 different physiological, behavioural and genetic mechanisms drive phenotypic variation on  
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29 which natural selection acts, (iii) allowing us to generate predictions about how differences in  
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31 susceptibility arise between individuals and populations, and finally aims to (iv) derive  
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33 general mechanistic insights by testing these predictions across a broad range of species.  
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40 The general feeling at the end of the Cornwall meeting was a combination of enthusiasm and  
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42 optimism, but also recognition of how much work there is ahead to establish a coherent  
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44 evolutionary understanding of early-life effects on health in humans. The first step of this  
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46 task is recognising the parallels between research in different fields, and the common aims of  
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48 our endeavours. We also need a common language and set of assumptions about how we test  
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50 for adaptations and how we think about evolutionary fitness in the field of human health.  
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53 Hopefully this collection of papers can help to tackle these first steps, and set the stage for  
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55 future cross-disciplinary research on the evolved mechanisms and functions of early life  
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57 effects.  
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**Overview of the issue**

The current issue closely follows this integrative approach that lies at the heart of evolutionary medicine to study early-life effects: to this end, the first three contributions of this issue heavily draw on evolutionary theory to predict how organisms should respond to environmental variation throughout the life course [16,30,31]: Gluckman and coworkers assess how different types of mismatches between a phenotype and environment can explain differences in disease aetiology [30], distinguishing between evolutionary and developmental mismatches. An evolutionary mismatch occurs when a novel environment is encountered that has never been experienced throughout evolutionary history. Suggested examples include the exposure of infants to formula milk (a novel evolutionary environment) as a substitute to breast milk, which is linked to increased rates of obesity and type 2 diabetes in later life [32]. By contrast, developmental mismatches reflect scenarios in which the cue received in early-life incorrectly predicts the future environment. Developmental mismatches build on long-standing ideas of predictive adaptive responses (PARs) and immediately adaptive responses (IARs), in which early-life cues are predictive about selective conditions in later life (PARs) or immediately after the cue has been received (IARs). For example, certain responses to early-life malnutrition (e.g., marasmus [33]) are likely to be predictive of the later-life nutritional environment, but will result in malprediction when individuals are faced with nutrition-rich diets later in life (often resulting in metabolic disorders [34]). They then discuss how evolutionary and developmental mismatches may differ in their mitigation.

Next, Frankenhuis et al [16] review the statistical structures of environments which are most conducive to the evolution of early-life effects (focusing particularly on PARs) by building

on previous analyses in the context of adaptive parental effects [35]. They review the recent flurry of evolutionary models on PARs, which highlight that environmental cues received in early life need to be sufficiently autocorrelated to later-life environments for such cues to be reliable. Moreover, less reliable cues may need to be sampled for longer, either selectively favouring longer sensitive periods for those cues that are more variable (e.g., [36]) or favouring no developmental plasticity at all [37]. They then highlight that most abiotic environments (e.g., temperature, rainfall) are, in fact, highly unpredictable (i.e., characterized by weak autocorrelations), raising the question whether PARs involve abiotic cues. Rather, Frankenhuis and coworkers suggest that more future work should focus on social environments -- in which the environment is shaped by the individual itself and other members of its social group -- as these are suggested to have much higher autocorrelations. Overall, the review by Frankenhuis suggests that future studies should aim to measure the much more aspects of environmental variation throughout an individual's life and beyond.

The call by Frankenhuis to consider the social environment also dovetails with a theoretical model by Kuijper & Johnstone [31], which considers why social behaviours are commonly found to depend on the level of social adversity experienced in early life. Focusing on an example scenario on the evolution of cooperative breeding, they show that the tendency to help others commonly evolves to depend on social experiences in early life. Moreover, this form of developmental plasticity can have intergenerational consequences: in taxa with nonoverlapping generations, a positive feedback occurs, where individuals who received little help themselves are found to be less likely to help others later in life, while individuals who received lots of help are more likely to help others later. Hence, this leads to intergenerational feedbacks where one's helping behaviour may resemble that of previous generations. The situation is, however, more complex in the context of nonoverlapping generations, where

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such feedbacks are negative instead, with individuals who received little help being more likely to help themselves later. Overall, the model adds weight to the consideration by Frankenhuys and coworkers [16] that social interactions and the composition of the social group should be considered more widely when studying the causes and consequences of developmental plasticity.

Wells [38] argues that the maternal phenotype itself may hamper the evolution of PARs: although offspring stand to benefit from extensive maternal investment during the initial most vulnerable stages of their lives, the flipside is that they open themselves up to investment strategies that benefit maternal, rather than offspring fitness [39]. Wells reviews evidence where interventions that overlook such differences between maternal and offspring optima can lead to counterintuitive outcomes: for example, a study performed in an Ethiopian population showed that the energy saving measure of installing water taps did not improve child nourishment as intended: rather, the higher energy levels resulted in a higher birth rate and subsequent offspring undernourishment [40]. To account for maternal impacts on early-life effects, Wells suggests a three-step model in which offspring developmental plasticity is initially influenced by the maternal phenotype, then the early-life external environment and finally the later-life selective environment. Wells suggests that such a three stage model is particularly important in scenarios where there is substantial inequality among mothers in resource availability (e.g., social hierarchies). To sum up, these four papers give overview of how evolutionary predictions of adaptation to environmental change lie at the forefront of thought in the study of early-life effects.

Continuing with this integrative approach, the issue then moves on to review the *mechanisms* that underlie the relationship between an environmental stimulus in early life and its the long-



term phenotypic consequences: in this context, Vukic et al. [19] review how DNA methylation, histone modification and RNA molecules are the major epigenetic mechanisms that mediate gene regulation changes in response to environmental exposures. While the majority of these modifications are reset either during the development of the primordial germ cells and during early embryonal development [41], some modifications can survive this reprogramming stage, potentially paving the way for long-term inheritance (e.g., [42]), although the scope for this is limited. Vukic et al discuss how nutritional influences and stress in mammalian model systems change epigenetic modifications; data on differential DNA methylation humans points in the same direction, although a causal link between epigenetic modifications and later-life phenotypes observed are yet to be made. Vukic et al make several recommendations for future analyses, noting in particular that repetitive regions are often excluded from bioinformatic analyses, whereas those regions appear to be particularly resistant to epigenetic reprogramming during development.

While most of the current work on intergenerational and transgenerational effects focuses on maternal transmission, Baxter and Drake [20] review recent research on the epigenetic mechanisms that facilitate transgenerational effects through fathers. An emerging message is that exposure of males to some (but not all) early-life environmental insults indeed affects epigenetic modifications in sperm. Moreover, also changes in the phenotypes of offspring sired by these males are observed. Yet, a causal link between sperm epigenetic modifications and offspring phenotypic variation is yet to be established: for example it is hitherto unknown whether and how paternally inherited histone modifications can indeed survive the epigenetic reprogramming stages in early development. More recent studies suggest that RNAs might well be the more important epigenetic mechanism that mediate paternal influences on the offspring's phenotype. However, Baxter and Drake also urge to consider other, non-

epigenetic mechanisms (e.g., paternal influences on maternal behaviour) with which fathers may affect offspring phenotypes and which currently receive little consideration.

Hormones are another major mechanism with which mothers influence offspring phenotypes. Hence, Groothuis and coworkers [43] focus on maternal hormones in avian systems. As the embryo develops outside the mother, birds are particularly amenable to the study of maternal effect hormones, illustrating why an integrative approach that relies on inferences taken across a broad range of species may provide insights above and beyond studies taking a singular, human-centered focus. Groothuis et al highlight that the time of postulating simple, univariate hypotheses about the phenotypic consequences of hormones is now well and truly over, urging for a framework that embraces the complexity inherent to hormone-mediated maternal effects. There is now an accumulating of studies that find that interactions among hormones themselves (or between hormones and other allocation components such as egg yolk), or trade-offs between costly investment in hormones and other allocation components prevail. Hence, this puts many evolutionary predictions which zoom in on maternal effects as a means to predict the prevalent environment in a new light, suggesting that a multivariate evolutionary theory of maternal hormones is needed to make sensible predictions in the face of this complexity.

Danchin and coworkers [44] provide how mechanisms of inheritance scenarios where epigenetic modifications or parental effects give rise to so-called transgenerational effects [45], where a phenotypic variant is transmitted for three generations or longer. The review highlights how our existing views of gene-centric inheritance need to be modified to accommodate for these transgenerational effects and what consequences this has for adaptation.

Following these mechanistic insights, we then move on to testing evolutionary predictions about early-life effects, both in the lab and the wild. Crucially, at the heart of evolutionary medicine lies a comparative approach, in which insights are obtained by comparing early-life effects and their consequences across multiple species. To this end, the current issue contains novel work on early-life effects in organisms ranging from nematode worms, cichlid fish, wild populations of meerkats and mongooses, to humans. Novel work from the lab of Rechavi [46] focuses on how exposure to liquid versus solid environments in the nematode model organism *Caenorhabditis elegans* has transgenerational effects on morphology lasting up to generation F3. Next, Reyes Contreras and coworkers [47] use pharmacological manipulations in a cooperatively breeding cichlid system (*Neolamprologus pulcher*) to causally determine how early-life modifications (mediated by stress hormones) determine the adult social phenotype.

The issue also includes two studies of early-life effects in wild animal populations. Studies of wild animals living in the environment in which they evolved are a powerful complement to laboratory studies of model organisms. They offer a way to measure the fitness impacts of variation in early life conditions, and test evolutionary hypotheses about the causes and consequences of developmental responses. Dantzer and coworkers [48] show that a manipulation of early-life maternal hormone exposure affects later-life cooperative behaviour in female, but not male, meerkats. Their findings suggest that these early life effects may be in the interests of parents, but not offspring. Vitikainen and coworkers [49] show that banded mongoose offspring that receive more care and attention from helpers during a six week period in early life are heavier at sexual maturity, and in the case of females, go on to produce more surviving offspring across their lifetime. These ‘durable benefits’ of care are manifested

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long after the initial helping act, often after the helper has died, which has important implications for the evolution of parental and alloparental care.

Studies of wild animals living in the environment in which they evolved are a powerful complement to laboratory studies of model organisms. They offer a way to measure the fitness impacts of variation in early life conditions, and the causes and consequences of individual variation in phenotype and physiology. Many of the tradeoffs involved in development may only be manifested in conditions exposed to natural predators and pathogens, and where resources are limited and heterogeneously distributed in time and space.

Next, Nicholas & Ozanne [50] review how mouse models allow one to study the mechanisms which mediate how maternal obesity affects metabolic programming in offspring and what interventions are likely to be most effective. Mice that have been given a high-fat diet (HFD) induce various metabolic changes in their offspring (e.g., increased adiposity, hyperinsulinemia/hyperglycaemia), where metabolic aberrations depend on the timing of maternal HFD exposure as well as on the sex of the offspring (potentially mediated by sex hormones). Underlying mechanisms may not only include metastable epialleles (such as the well studied agouti viable yellow locus  $A^{vy}$  and others [51]), but Nicholas & Ozanne also raise the exciting possibility that epigenetic modifications in the mtDNA play a role in metabolic programming.

In human populations, Fall & Kumaran [5] review patterns of metabolic programming in humans, current knowledge about the effect of interventions and the underlying epigenetic mechanisms. Key areas of research focus on the long-term consequences of fetal

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3 undernutrition, carryover effects of maternal overweight and diabetes and how this relates to  
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5 patterns of post-natal weight gain. A general finding is that the highest risk of metabolic  
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7 disease is consistently found in those individuals who started off with a low birth weight, but  
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9 became relatively heavy in later life. Fall & Kumaran [5] highlight that most studies that  
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11 assessed the effect of metabolic interventions in early-life lack follow-up studies throughout  
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13 the life course of children. In case a follow-up study exists, evidence that interventions affect  
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15 metabolic outcomes in offspring is mixed. As it emerges that many early-life effects originate  
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17 around the time of conception [4], Fall & Kumaran [5] suggest that future studies should  
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19 focus on an earlier timing of these interventions (e.g., before or during conception).  
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22 Regarding the study of the underlying mechanisms, Fall & Kumaran [5] also stress that  
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24 despite accumulating research, there are currently no studies in humans that have  
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26 demonstrated the full chain of events, starting from an intervention which results in an  
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28 epigenetic modification to modifications in gene expression and a resulting disease-related  
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38 As undertaking such causal studies will be difficult in humans, Hannon et al [52] use an  
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40 epigenomic association study (EWAS; [53]) to assess whether epigenomic modifications  
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42 mediate the relationship between maternal smoking and offspring birth weight. To this end,  
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44 they exploit an existing collection of neonatal blood spot samples collected shortly after birth  
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46 from over 1300 neonates. Measuring differential DNA methylation, they find 18  
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48 differentially methylated positions (DMPs) that are associated with birth weight, and 110  
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50 DMPs which are associated with maternal smoking. They then use a mediator-approach ,  
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52 derived from structural equation modelling [54], to find that three DMPs are likely to mediate  
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54 how maternal smoking affects low birth weight, shedding light on the mechanism with which  
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56 early-life environmental insults change regulation. They suggest that differential DNA  
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methylation, when measured as early as possible in life, can serve as biomarkers of early-life exposure that would be highly valuable to the study of early-life effects.

The studies by Sear et al [55] and Williams & Drake [56] use published data on human health and fertility from across the globe to evaluate evidence that human life history has been shaped by adaptive early-life effects. Sear et al [55] examine the relationship between father absence and age at first menarche in girls, and in particular the hypothesis that father absence should be associated with earlier age at menarche because it is an indicator of an unstable social environment [57]. Sear et al [55] show that previous empirical support for this hypothesis is largely restricted to WEIRD human datasets (Western, Educated, Industrialised, Rich, Democratic [58]), and that data on hunter gatherers and other small scale human societies offer a more complex picture. Williams & Drake [56] present a wide-ranging review of the literature on preterm birth (i.e. birth prior to week 37 of gestation) and ask whether variation in rates of preterm birth and its consequences can be explained if early birth is an ‘immediate’ adaptive response to conditions experienced *in utero*, or a predictive adaptive response to anticipated future conditions. They show that preterm birth is associated with predictable changes in adult physiology. However, as with many other studies, testing whether these changes are adaptive remains difficult given the lack of detailed information about life history trajectories and fitness in human datasets.

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